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In Situ Generated Fluorinated Iminium Salts for Difluoromethylation and Difluoroacetylation

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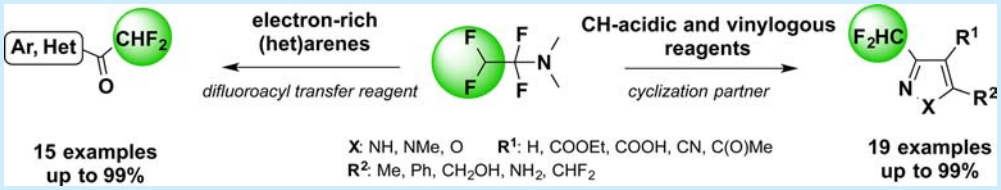
Supporting Information



ABSTRACT: The use of TFEDMA, a fluoroalkyl amino reagent, for the difluoromethylation and difluoroacylation of arenes, heteroarenes, and C−H acidic compounds is reported. This approach allows for an efficient access to difluoromethylated products of high added value in good to excellent yields and with scale-up possibilities.

Today, organofluorine compounds play a key role in life science oriented research.[1] In small molecule research (SMR) in medicinal and agricultural sciences, fluoroalkyl units are popular functional groups as they can improve the binding affinity, the physicochemical properties, and the metabolic stability of molecules.[1a,2] The incorporation of a difluoromethyl group (−CF_2H) into organic molecules has become highly attractive due to its hydrogen-bonding potency.[1a,2a,3] In addition, the CF_2H group is a more lipophilic H-bond donor than either an OH or NH, offering the potential for improved membrane permeability.

The difluoromethylation of aromatics or heteroaromatics is often based on the reaction of aldehydes with SF_4, a highly toxic gas requiring specialized equipment, or with aminosulfur trifluorides (e.g., DAST, Deoxofluor), which cannot be easily employed on an industrial scale.[4] In addition, a lack of functional group tolerance and/or harsh reaction conditions is a real synthetic restriction. Although recent years have witnessed the development of good methods, in particular organometallic ones, for the late-stage installation of trifluoromethyl groups,[2b,5] difluoromethylation is still in its infancy. Amii reported, for example, the Cu-catalyzed cross-coupling of α-trialkylsilyl difluoroacetates with aryl iodides.[6] Baran et al. developed the radical difluoromethylation of heteroaromatic compounds with zinc difluoromethanesulfinate $Zn(SO_2CF_2H)_2$.[7] Hartwig[8] and Qing[9] succeeded in the difluoromethylation of arenes and heteroarenes with Cu−CF_2H. Prakash et al. reported on the use of copper iodide and Bu_3SnCF_2H.[10] Finally, Gooßen disclosed an elegant Sandmeyer-type difluoromethylation process.[11] Nevertheless, there is still a tremendous need for efficient methods for the introduction of the CF_2H unit under industrially compatible conditions.

In the present work, we report access to a variety of difluoromethylated and difluoroacylated building blocks. The reactions are based on the in situ preparation of difluoromethylated iminium salts via Lewis acid mediated activation of 1,1,2,2-tetrafluoro-*N*,*N*-dimethylethan-1-amine (**1a**; TFEDMA). TFEDMA belongs to the so-called fluoroalkyl amino reagents (FAR). So far, three of them are commercially available, i.e., TFEDMA (**1a**), *N*,*N*-diethyl-2-chloro-1,1,2-trifluoroethan-1-amine (Yarovenko reagent), and *N*,*N*-diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine (Ishikawa reagent).[12] They can be readily prepared from commercially available bulk fluoro olefins (chemicals frequently employed for polymers) by a hydroamination reaction.[13]

TFEDMA and its congeners are effective reagents for the conversion of R−OH into R−F. The utility of TFEDMA has recently been reviewed,[14] and efforts have been undertaken to extend its scope to different types of reaction.[15] Very recently, we became interested in the use of FAR's in the synthesis of difluoromethylated pyrazoles and developed two different approaches toward them.[16] The reactivity of these fluoroalkylamines is based on a negative hyperconjugation between the nitrogen lone pair of the amino group and the adjacent difluoromethyl group (see **1b** in Scheme 1). It has been shown that TFEDMA affords, after activation with a Lewis acid like BF_3·Et_2O, an iminium salt such as **1c** with Vilsmeier-type reactivity (Scheme 1). Based on our previous studies, we were convinced

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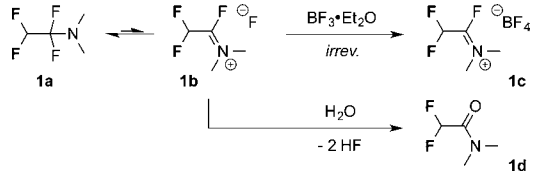
Scheme 1. TFEDMA (1a), Iminium Form (1b), Activated Iminium Salt (1c), and Acetamide (1d) Resulting from Hydrolysis

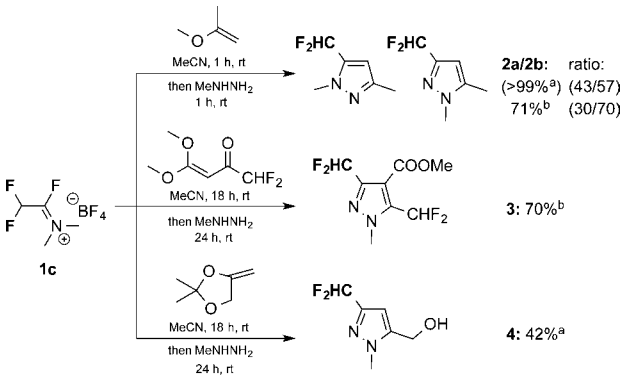


that FARs could be further exploited for the introduction of $-CF_2H$ groups (or analogues). In fact, for the introduction of a difluoromethyl fragment at an early stage, one can employ either difluoroacetyl chloride (difficult to prepare, low boiling, and rather air- and moisture- sensitive), difluoroacetic anhydride (expensive and one loses 0.5 equiv in the synthesis), or ethyl difluoroacetate (which requires further activation with organometallic reagents or strong bases).

Therefore, we decided to study the reactivity of activated TFEDMA **1c** toward various substrates and to investigate its scope and limitations for the synthesis of difluoromethylated building blocks. Compound **1c** could be isolated after activation of TFEDMA **1a** with $BF_3{\cdot}Et_2O$ in anhydrous CH_2Cl_2 or Et_2O and stored several days as a stable reagent under inert atmosphere in the refrigerator or more conveniently directly used after quick activation in dry MeCN.

First, we studied the reactivity of activated TFEDMA toward vinyl ethers and ketene acetals which reacted smoothly and afforded, after cyclization of the intermediates with hydrazine, the corresponding pyrazoles in good to excellent yields (Scheme 2). When **1c** was reacted with 2-methoxypropene and further

Scheme 2. Reaction of Activated TFEDMA 1c with Vinyl Ethers

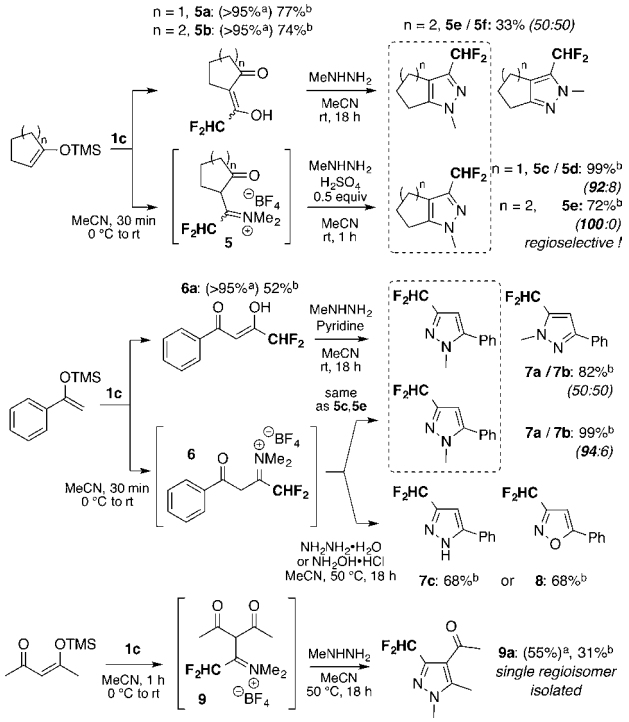


[a]F NMR yield using PhF as internal standard. [b]Isolated yield.

cyclized with methyl hydrazine, a pair of regioisomers **2a**/**2b** in a 43:57 ratio was obtained quantitatively. Similarly, **1c** reacted with a ketene acetal (1,1-difluoro-4,4-dimethoxybut-3-en-2-one[17]) and in situ cyclized with methyl hydrazine to afford 3,5-bis(difluoromethyl)pyrazole **3**. 2,2-Dimethyl-4-methylene-1,3-dioxolane led to the one-pot formation of 3-(difluoromethyl)-5-(hydroxymethyl)pyrazole **4** in moderate yield.

Next, we studied the reactivity of activated TFEDMA **1c** toward silyl enol ethers (Scheme 3). The commercially available silyl enol ethers of cyclopentanone and cyclohexanone were reacted with the iminium salt **1c** affording the difluorohydroxyethylidene cycloalkyl ketones **5a**,**b**. They were rather tedious to

Scheme 3. Reaction of Activated TFEDMA 1c with Silyl Enol Ethers



[a]Conversion by ^{1}H NMR. [b]Isolated yield.

purify and were prone to degradation. When treated with methyl hydrazine, **5a**,**b** cyclized to a 1:1 mixture of the corresponding bicyclic compounds **5e**/**5f**. Fortunately, in situ cyclization of the iminium intermediate **5** allowed for the regioselective synthesis of **5c** (92:8) and **5e** (one regioisomer).

The silyl enol ether of acetophenone similarly reacted with **1c**, and X-ray crystallographic analysis of **6a**[18] revealed a *Z* configuration (Figure 1).[19] When **6a** was reacted with methyl

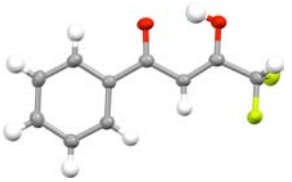


Figure 1. Crystallographic structure of **6**.[19]

hydrazine, a 1:1 pair of *N*-methylpyrazoles **7a** and **7b** was obtained. Once again, in situ cyclization of the iminium salt **6** afforded *N*-methylpyrazole **7a** in excellent regioselectivity (94:6). The reaction with hydrazine hydrate and hydroxylamine·HCl provided pyrazole **7c** and isoxazole **8** in 68% yield each. The silyl enol ether of acetylacetone gave methyl pyrazole **9a** as one single regioisomer after in situ cyclization of the iminium salt **9** with methyl hydrazine (Scheme 3).

Next, we investigated the reaction of activated TFEDMA **1c** with various CH-acidic compounds, namely malononitrile and ethyl cyanoacetate, in order to access the corresponding difluoro(dimethylamino)ethylidenes **10** and **11** (Scheme 4).

The best results were obtained when **1c** was combined with the CH-acidic compound and the mixture rapidly treated with Hünig's base (DIPEA). The products **10** and **11** were efficiently

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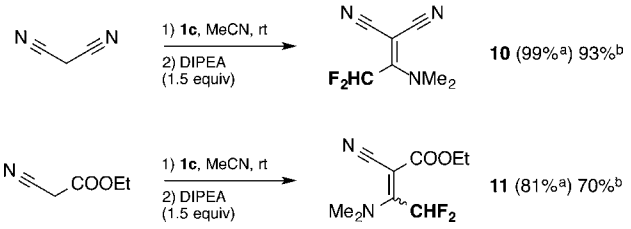
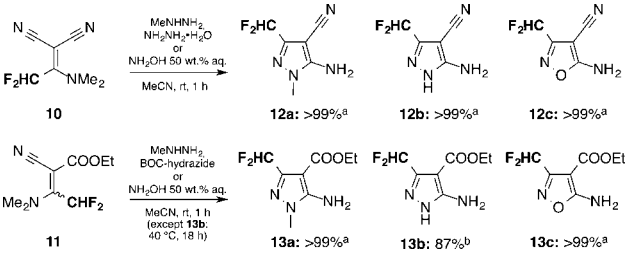
Scheme 4. Reaction of Activated TFEDMA 1c with Malononitrile and Ethyl Cyanoacetate



[a]^{19}F NMR yield using PhF as internal standard. [b]Isolated yield.

converted into difluoromethylated 5-aminopyrazoles. Methyl hydrazine afforded the *N*-Me pyrazoles **12a** and **13a** in almost quantitative yield. A similar result was obtained for the reaction of **10** with hydrazine hydrate yielding the NH-pyrazole **12b**. In contrast, **11** led to NH-pyrazole **13b** in a low 44% yield. The yield was improved to 87% by employing BOC-hydrazide instead of hydrazine hydrate (Scheme 5). When the cyclization was

Scheme 5. Synthesis of 3-(Fluoroalkyl)-5-aminopyrazoles and -isoxazoles



[a]^{19}F NMR yield using PhF as internal standard. [b]Isolated yield.

performed with hydroxylamine, the corresponding isoxazoles **12c** and **13c** were obtained almost quantitatively. The structures of **10** and **13c** were confirmed by single-crystal X-ray diffraction (Figure 2).[19] In the case of the *N*-methylpyrazoles **12a** and **13a**,

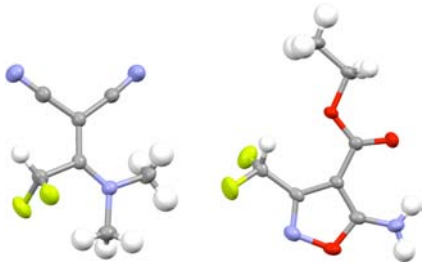


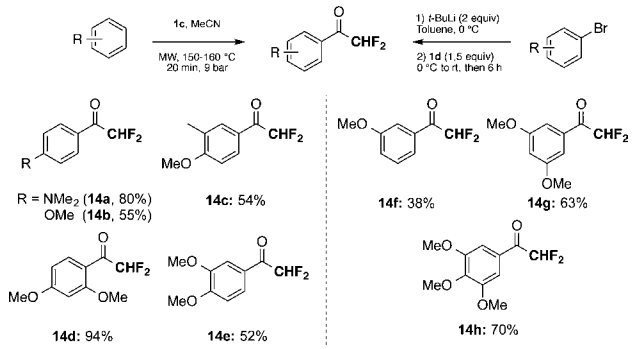
Figure 2. Crystallographic structure of **10** (left) and **13c** (right).[19]

the regioselectivity was evaluated as 99:1 and the structure of isolated products confirmed by ^{1}H/^{13}C HMBC experiments (correlations between N-CH_3 protons and C-NH_2 carbon).

Finally, we studied the use of activated TFEDMA **1c** as a difluoroacyl transfer reagent for aromatic and heteroaromatic compounds. Wakselman reported in 1975 on the use TFEDMA and its analogues with electron-rich aromatics.[15c] *N,N*-Diethylaniline, *N,N*-dimethyl-*m*-toluidine, 1-(dimethylamino)-naphthaline, indole, thiophene, and *N*-methylpyrrole underwent difluoroacylation in low yields with limited substrate scope.[12a−c]

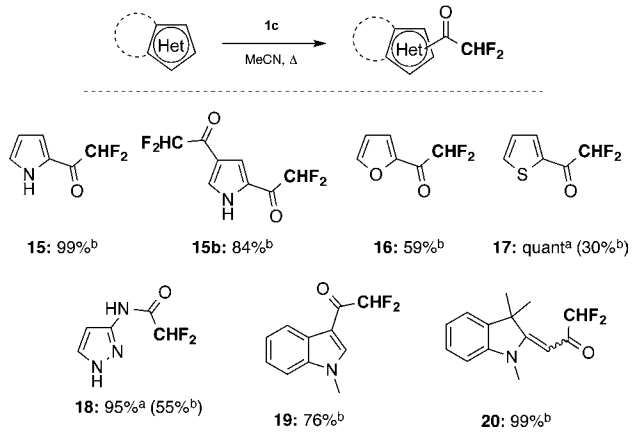
We were able to extend the scope of this reaction for the difluoroacylation of arenes by employing either microwave assistance or the reaction of organolithiums. When **1c** and the desired arene were heated in MeCN for 20 min under an inert atmosphere, using microwave irradiation, a series of difluoroacylated aromatics with electron-donating group(s) (**14a−e**) such as OMe, NMe_2, Me, etc. became accessible in good to excellent yields with a regioselectivity governed by the substituents (Scheme 6). To overcome the regioselectivity issues and to

Scheme 6. Using TFEDMA as Difluoroacylating Agent for Arenes



broaden the substrate scope, we demonstrated that halogen/metal interconversions could be employed to convert aryl halides into difluoroacyl derivatives. In fact, bromine/lithium exchange followed by trapping with *N,N*-dimethyldifluoroacetamide (**1d**) (derived from TFEDMA by hydrolysis) provided the desired difluoroacylated products **14f−h** in good yields (Scheme 6). Several electron-rich heterocycles were also successfully difluoroacylated (Scheme 7). Pyrrole afforded compound **15a**

Scheme 7. Difluoroacylation of Electron-Rich Heterocycles



[a]Conversion by ^{1}H NMR. [b]Isolated yield.

with **1c**, which in turn could be difluoroacylated to give **15b**. Furan reacted with **1c** to give the highly sensitive and volatile product **16**. Thiophene gave quantitatively the volatile derivative **17**, and 3-aminopyrazole provided compound **18** in good yield.

As expected, both pyrazole and imidazole were unreactive toward **1c**. Nitrogen-based benzo-fused heterocycles like indoles and methylene indolines were efficiently difluoroacylated using **1c**, providing compounds **19** (see crystallographic structure in Figure 3)[19] and **20** in excellent yields. In contrast, oxygen-based precursors like benzofuran were not compatible with this reaction.

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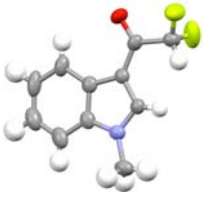

Figure 3. Crystallographic structure of **19**.[19]

In summary, we have shown that upon Lewis acid activation TFEDMA (1,1,2,2-tetrafluoro-*N*,*N*-dimethylethan-1-amine, **1a**) reacts efficiently with alkyl or silyl enol ethers, C−H acidic derivatives like malonitriles, and cyanoacetates to afford highly valuable building blocks. We were also able to develop an efficient method for the difluoroacylation of aromatics that used either microwave irradiation or organolithium chemistry and of heteroaromatics using conventional heating. This new methodology, which employs easily accessible and inexpensive starting materials, can be scaled up and used in industrial applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02184.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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(19) CCDC 1415347 (**6**), 1415348 (**13c**), 1415349 (**10**), and 1415350 (**19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif, 2015.

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